

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 02 JUN 2006

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Applicant's or agent's file reference HTP-P01374WO	<b>FOR FURTHER ACTION</b>		See Form PCT/IPEA/416
International application No. PCT/EP2005/001298	International filing date (day/month/year) 09.02.2005	Priority date (day/month/year) 09.02.2004	
International Patent Classification (IPC) or national classification and IPC INV. C12N15/11 A61K31/7088 A61P25/00 C07K14/71 C12Q1/68 G01N33/50 G01N33/68			
Applicant REGENION GMBH			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 22 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> <i>sent to the applicant and to the International Bureau</i> a total of 9 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input checked="" type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only)</i> a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand  20.07.2005		Date of completion of this report  01.06.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized officer  Macchia, G  Telephone No. +31 70 340-4078	



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## Box No. I Basis of the report

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1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
  - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
    - ☐ international search (under Rules 12.3(a) and 23.1(b))
    - ☐ publication of the international application (under Rule 12.4(a))
    - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements**\* of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

### Description, Pages

1-38 as originally filed

### Sequence listings part of the description, Pages

49-115 received on 23.02.2005 with letter of 21.02.2005

### Claims, Numbers

1-27 received on 29.04.2006 with letter of 26.04.2006

### Drawings, Sheets

1/5-5/5 as originally filed

- ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☒ the claims, Nos. 1
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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## Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,  
☒ claims Nos. 8-13, 21, 26, all with respect to industrial applicability,

because:

- ☒ the said international application, or the said claims Nos. 8-13, 21-26, all with respect to industrial applicability, relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).
- ☐ no international search report has been established for the said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

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## Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:
  - ☒ restricted the claims.
  - ☐ paid additional fees.
  - ☐ paid additional fees under protest and, where applicable, the protest fee.
  - ☐ paid additional fees under protest but the applicable protest fee was not paid.
  - ☐ neither restricted the claims nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:
  - ☐ complied with.
  - ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
  - ☒ all parts.
  - ☐ the parts relating to claims Nos. .

## Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes: Claims	7-13, 17-26
	No: Claims	1-6. 14-16, 27
Inventive step (IS)	Yes: Claims	
	No: Claims	1-27
Industrial applicability (IA)	Yes: Claims	1-7, 12-20, 27
	No: Claims	

### 2. Citations and explanations (Rule 70.7):

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

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**Supplemental Box relating to Sequence Listing**

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**Continuation of Box I, item 2:**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:
  - a. type of material:
    - ☒ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☒ on paper
    - ☒ in electronic form
  - c. time of filing/furnishing:
    - ☒ contained in the international application as filed
    - ☐ filed together with the international application in electronic form
    - ☒ furnished subsequently to this Authority for the purposes of search and/or examination
    - ☐ received by this Authority as an amendment\* on
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

\* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

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Reference is made to the following documents:

- D1: WO 93/19783 A (THE WHITTIER INSTITUTE FOR DIABETES AND ENDOCRINOLOGY (US); LOGAN Ann; BAIRD Andrew) 14 October 1993;
- D2: LESNÉ S. et al.: "Transforming Growth Factor- $\beta$ 1 potentiates Amyloid- $\beta$  generation in astrocytes and in transgenic mice " THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 278, no. 20, 16 May 2003, pages 18408-18418;
- D3: SÁNCHEZ-CAPELO A. et al.: " Transforming Growth Factor  $\beta$ 1 overexpression in the nigrostriatal system increases the dopaminergic deficit of MPTP mice " MOLECULAR AND CELLULAR NEUROSCIENCE, vol. 23, 2003, pages 614-625;
- D4: EP-A-1 133 988 (BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK mbH (DE); SCHLINGENSIEPEN Karl-Hermann.; SCHLINGENSIEPEN Reimar) 19 September 2001;
- D7: ZHAO J. et al.: " Abrogation of Transforming Growth Factor- $\beta$  type II receptor stimulates embryonic mouse lung branching morphogenesis in culture " DEVELOPMENTAL BIOLOGY, vol. 180, 1996, pages 242-257;
- D13: KRIEGLSTEIN K. et al.: " Reduction of endogenous Transforming Growth Factor  $\beta$  prevents ontogenetic neuron death " NATURE NEUROSCIENCE, vol. 3, no. 11, November 2000, pages 1085-1090;
- D14: HIGASHIYAMA M. et al.: " Inhibition by Transforming Growth Factor- $\beta$ 1 of the cellular action of Arginine Vasopressin in cultured rat glomerular mesangial cells " HYPERTENSION RESEARCH, vol. 22, no. 3, 1999, pages 173-180;
- D15: BAKER C.A. et al.: " Microglial activation varies in different models of Creutzfeldt-Jakob disease " JOURNAL OF VIROLOGY, vol. 73, no. 6, June 1999, pages 5089-5097;
- D16: WYSS-CORAY T. et al.: " Chronic overproduction of Transforming Growth Factor- $\beta$ 1 by astrocytes promotes Alzheimer's disease-like microvascular degeneration in transgenic mice " AMERICAN JOURNAL OF PATHOLOGY, vol. 156, no. 1, January 2000, pages 139-150;

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- D17: DE GROOT C.J.A. et al.: " Expression of Transforming Growth Factor (TGF)- $\beta$ 1, - $\beta$ 2, and - $\beta$ 3 isoforms and TGF- $\beta$  type I and type II receptors in Multiple Sclerosis lesions and human adult astrocytes cultures " JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, vol. 58, no. 2, February 1999, pages 174-187.
- D18: WO 03/000656 A (ISIS PHARMACEUTICALS, INC. (US); MURRAY Susan F.; WYATT Jacqueline R.) 3 January 2003;
- D19: YU W. et al.: " Evidence for role of Transforming Growth Factor- $\beta$  in RRR- $\alpha$ -Tocopheryl Succinate-induced apoptosis of human MDA-MB-435 breast cancer cells " NUTRITION AND CANCER, vol. 27, no. 3, 1997, pages 267-278;
- D20: LUO X. et al.: " The expression of Smads in human endometrium and regulation and induction in endometrial epithelial and stromal cells by Transforming Growth Factor- $\beta$  " THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 88, no. 10, 2003, pages 4967-4976;
- D21: LENFERINK A.E.G. et al.: " Expression of TGF- $\beta$  type II receptor antisense RNA impairs TGF- $\beta$ 1 signaling *in vitro* and promotes mammary gland differentiation *in vivo* " INTERNATIONAL JOURNAL OF CANCER, vol. 107, 2003, pages 919-928;
- D22: MILNER N. et al.: " Selecting effective antisense reagents on combinatorial oligonucleotide arrays " NATURE BIOTECHNOLOGY, vol. 15, 1997, pages 537-541;
- D23: YEE W. et al.: " Glucocorticoid-induced tropoelastin expression is mediated via transforming growth factor- $\beta$ 3 " AMERICAN JOURNAL OF PHYSIOLOGY. Lung Cellular and Cellular Physiology, vol. 270, no. 14, 1996, pages L992-L1001;
- D24: LUO J. et al.: " Growth factor-mediated neural proliferation: target of ethanol toxicity " BRAIN RESEARCH REVIEWS, vol. 27, 1998, pages 157-167;
- D25: LUO J. et al.: " Basic fibroblast growth factor- and platelet-derived growth factor-mediated cell proliferation in B104 neuroblastoma cells: effects of ethanol on cell cycle kinetics " BRAIN RESEARCH, vol. 770, 1997, pages 139-150.

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The documents D24 and D25 were not cited in the international search report.

Copies of the documents are appended hereto.

**Re Item I**

**Basis of the Report**

I-1). The statement in claim 1: " with the proviso that said oligonucleotide is not 5'-CAGCCCCCGACCCATGGCAG-3' " has no basis in the application as originally filed.

Therefore, this statement introduces subject-matter which goes beyond that of the application as originally filed, contrary to Article 34(2)(b) PCT (Rule 70.2(c) PCT).

Consequently, this statement in claim 1 was not taken in account in present Report.

In this respect, it should however be remarked that the oligonucleotide 5'-CAGCCCCCGACCCATGGCAG-3', which the Applicant tried to exclude from claim 1, is not embraced by the general formula 5'-XCAGCCCCCGACCCATGZ-3' because this oligonucleotide does not have any residue corresponding to position " X ", whilst, according to the terms of claim 1, this term " X " should comprise at least one oligonucleotide residue.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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III-1). Claims **8-11** and **21-26** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT; Article 33(4) PCT).

**Re Item IV**

**Lack of unity of invention**

This Authority considers that there are 2 inventions covered by the claims indicated as follows:

- I: claims 1-14, related to oligonucleotides directed against TGF- $R_{II}$ , pharmaceutical preparations, uses and methods related thereto.
- II: claims 15-27, related to oligonucleotides directed against TGF- $R_I$ , pharmaceutical preparations, uses and methods related thereto.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

the common concept underlying the inventions disclosed in present application is that inhibition of TGF $\beta$  / TGF $\beta$  receptors signalling can have therapeutical applications in neuronal diseases.

This common concept is not novel (Rule 13.1 PCT): document D1 discloses the use of neutralizing anti-TGF-1 antibodies and other TGF-1-neutralizing agents in therapy of

diseases wherein neurogenesis or neuroregeneration has a beneficial effect (D1: see relevant passages throughout the entire document).

A role for TGF $\beta$  / TGF $\beta$  receptors signalling in neurological disorders is also suggested in the following documents: document D3 states that *an increase of TGF- $\beta$ 1 levels ... may be a risk factor for the development of Parkinson's disease* (D3: abstract and relevant passages throughout the entire document). Document D2 states that *TGF- $\beta$ 1 potentiates A $\beta$  production in human astrocytes and may enhance the formation of plaques burden in the brain of Alzheimer's disease patients* (D2: abstract and relevant passages throughout the entire document; see also the disclosure of D16). Document D13 shows that reduction of TGF $\beta$  through TGF $\beta$ -R $_{II}$  fusion protein prevents ontogenetic neuron death (D13: abstract and relevant passages throughout the entire document). Document D15 states that *TGF- $\beta$ 1 can be an essential signal for amyloid deposition* (D15: abstract and relevant passages throughout the entire document). Document D17 suggests a detrimental role for TGF- $\beta$  in MS pathology rather than a disease-limiting role (D17: page 186). Moreover, on page 186, D17 suggests a therapeutical application of TGF- $\beta$  receptor antagonists.

Antisense technology is well known to the person skilled in the art as a mean to reduce expression of a certain gene, and therapeutical applications of antisense molecules are well established in the technical field. Indeed, documents D7, D14, D19 and D20 describe antisense oligonucleotides directed against the TGF- $\beta$  type II receptor as a mean to abrogate TGF- $\beta$ 1 signalling (D7, D14, D19, D20: abstract and relevant passages throughout the entire documents). Document D21 describes that inhibition of expression of the TGF- $\beta$  type II receptor by means of transfection with an antisense TGF- $\beta$  type II receptor construct abrogates TGF- $\beta$ 1 signalling (D21: abstract and relevant passages throughout the entire document). Document D23 describes an antisense oligonucleotide directed against the TGF- $\beta$  type I receptor as a mean to abrogate TGF- $\beta$ 1 signalling (D23:

relevant passages throughout the entire document).

In the light of this prior art, it should be concluded that the special technical feature, within the meaning of Rule 13.2 PCT, of each of the inventions listed above, is indeed the target of the oligonucleotides concerned in present application, which is unique for each of the inventions and not shared among the inventions.

Therefore, due to the fact that it was already known that TGF $\beta$  / TGF $\beta$  receptor signalling was involved in neurological disorders, due to the difference in the primary structure of the target molecules concerned in present application, and due to the fact that no other technical feature can be distinguished which, in the light of the prior art, could be regarded as special, common technical feature, the IPEA is of the opinion that there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.2 PCT.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement**

**Concerning invention 1 (TGFR<sub>II</sub>)**

V.1). Document D18 describes TGF $\beta$ -R<sub>II</sub> antisense oligonucleotides (D18: pages 88-90, table 1).

The oligonucleotide indicated in D18 as SEQ ID NO:20 and the oligonucleotide

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claimed in present application as SEQ ID NO:33 are 100% identical, over their entire length.

Moreover, some other oligonucleotides disclosed in table 1 of D18 overlap with some of the oligonucleotides claimed in present application, according to the following scheme:

D18 oligonucleotides	overlap with	present application's oligonucleotides
SEQ ID NO:20		SEQ ID NOs:3, 29-32, 34-72
SEQ ID NO:48		SEQ ID NOs:3, 29-72
SEQ ID NO:22		SEQ ID NO:27
SEQ ID NO:26, SEQ ID NO:27		SEQ ID NO:28
SEQ ID NO:28		SEQ ID NO:23, SEQ ID NO:5
SEQ ID NO:53		SEQ ID NO:16
SEQ ID NO:55		SEQ ID NO:21
SEQ ID NO:57		SEQ ID NO:17, SEQ ID NO:22
SEQ ID NO:58		SEQ ID NO:18
SEQ ID NO:65, SEQ ID NO:66		SEQ ID NO:26

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SEQ ID NO:73

SEQ ID NO:14

SEQ ID NO:81

SEQ ID NO:12

Other compounds concerned in present claim 5 are also disclosed in D18 (D18: page 14).

The subject-matter of claims **1** (related to mimetics and variants), **2** (insofar as SEQ ID NO:3, 34-36, due to the term " comprising ", and overall mimetics and variants are concerned), **3** (insofar as SEQ ID NOs:3, 34-36, due to the term " comprising ", and overall mimetics and variants are concerned) and **4-6** is therefore not novel (Article 33(2) PCT). In this respect, it should be noted that the terms " mimetics " and " variants " do not allow to distinguish the subject-matter to which they refer from the disclosure of D18.

V.2). Document D24 shows that ethanol does not antagonize the growth-inhibiting effect of TGF $\beta$ 1 on B104 cells, which are to be considered neuronal precursor cells (D24: page 162; see also D25: abstract).

The subject-matter of claim **14**, insofar as proliferation of neuronal precursor cells is concerned, is therefore not novel (Article 33(2) PCT).

V.3). Claims **1** (except for the subject-matter related to mimetics and variants), **2** (insofar as SEQ ID NOs:4-32 and 37-72 are concerned), **3** (insofar as SEQ ID NOs:41-44, 49-51, 56, 57 and 62 are concerned), **7-13** and **14** (insofar as expression of active TGFR<sub>II</sub> is concerned) formally meet the requirements of Article 33(2) PCT because their subject-matter was not disclosed in the available prior art.

V.4). Document D18, which is considered to represent the most relevant state of the art for the subject-matter of claims 1-3, discloses TGF $\beta$ -R<sub>II</sub> antisense oligonucleotides.

The subject-matter of claims **1, 2** (insofar as SEQ ID NOs:4-32 and 37-72 are concerned), **3** (insofar as SEQ ID NOs:41-44, 49-51, 56, 57 and 62 are concerned), differs from the disclosure of D18, in that oligonucleotides comprising a certain sequence are concerned.

The problem to be solved by the present invention may therefore be regarded as the provision of further TGF-R<sub>II</sub> antisense oligonucleotides.

The solution proposed in claims 1, 2 (insofar as SEQ ID NOs:5, 12, 14, 16-18, 21-23, 26-32, 37-72 are concerned), 3 (insofar as SEQ ID NOs:41-44, 49-51, 56, 57, 62 are concerned) of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: an antisense oligonucleotide which differs from one already characterized (*i.e.* the ones of D18 overlapping with the ones of present application, according to the scheme above) by being few bases longer or shorter, or by being shifted in the region of recognition by few bases, is considered as non involving an inventive step (Article 33(3) PCT) because such an oligonucleotide is merely one of several straightforward possibilities from which the skilled person would select, once identified a candidate region suitable for antisense targeting, and in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

The subject-matter of claims **1, 2** (insofar as SEQ ID NOs:5, 12, 14, 16-18, 21-23, 26-32, 37-72 are concerned) and **3** (insofar as SEQ ID NOs:41-44, 49-51, 56, 57, 62 are

concerned) does therefore not involve an inventive step (Article 33(3) PCT).

- V.5). The subject-matter of claim **2** (insofar as SEQ ID NOs:4, 6-11, 13, 15, 19, 20, 24, 25 are concerned) does also not meet the requirements of Article 33(3) PCT because retrieving antisense molecules falling within the scope of claim 2 is a routine procedure, well known to the person skilled in the art and well established in the technical field (see for example the disclosure of document D22).

**Concerning invention 2 (TGFR<sub>I</sub>)**

- V.6). Document D23 describes an antisense oligonucleotide directed against the TGF- $\beta$  type I receptor as a mean to abrogate TGF- $\beta$ 1 signalling (D23: relevant passages throughout the entire document).

The subject-matter of claims **15** and **16** is therefore not novel (Article 33(2) PCT).

- V.7). Document D24 shows that ethanol does not antagonize the growth-inhibiting effect of TGF $\beta$ 1 on B104 cells, which are to be considered neuronal precursor cells (D24: page 162; see also D25: abstract)).

The subject-matter of claim **27**, insofar as proliferation of neuronal precursor cells is concerned, is therefore not novel (Article 33(2) PCT).

- V.8). Claims **17-26** and **27** (insofar as expression of active TGFR<sub>I</sub> is concerned) formally meet the requirements of Article 33(2) PCT because their subject-matter was not disclosed in the available prior art.

V.9). Document D23 is considered to represent the closest prior art for the subject-matter of claim 17.

The subject-matter of claim 17 differs from the disclosure of D23 in that other antisense oligonucleotide directed against the TGF- $\beta$  type I receptor are concerned.

The problem to be solved may therefore be regarded as the provision of further antisense oligonucleotide directed against the TGF- $\beta$  type I receptor.

The solution to this problem, as claims in present claim 17 cannot be considered as involving an inventive step (Article 33(3) PCT) because retrieving antisense molecules falling within the scope of claim 17 is a routine procedure, well known to the person skilled in the art and well established in the technical field (see for example the disclosure of document D22).

### **Concerning both inventions 1 and 2**

V.10). The document D3 is regarded as being the closest prior art for the subject-matter of claims 7-13 and 18-26, insofar as these claims are directed (implicitly or explicitly) to therapy of Parkinson's disease, and states that *an increase of TGF $\beta$ 1 levels ... may be a risk factor for the development of Parkinson's disease* (D3: abstract and relevant passages throughout the entire document).

The subject-matter of claims 7-13 and 18-26 differs from the disclosure of D3 in that the use of antisense oligonucleotides toward TGF-R<sub>II</sub> or TGF-R<sub>I</sub> for the therapy of Parkinson's disease is concerned.

- V.11). The document D2 is regarded as being the closest prior art for the subject-matter of claims 7-13 and 18-26, insofar as these claims are directed (implicitly or explicitly) to therapy of Alzheimer's disease and Dementia, and states that *TGFβ1 potentiates Aβ production in human astrocytes and may enhance the formation of plaques burden in the brain of Alzheimer's disease patients* (D2: abstract and relevant passages throughout the entire document; see also the disclosure of D16).

The subject-matter of claims 7-13 and 18-26 differs from the disclosure of D2 in that the use of antisense oligonucleotides toward TGF-R<sub>II</sub> or TGF-R<sub>I</sub> for the therapy of Alzheimer's disease and Dementia is concerned.

- V.12). The document D15 is regarded as being the closest prior art for the subject-matter of claims 7-13 and 18-26, insofar as these claims are directed (implicitly or explicitly) to therapy of Creutzfeldt-Jakob's disease, and states that *TGFβ1 can be an essential signal for amyloid deposition* (D15: abstract and relevant passages throughout the entire document).

The subject-matter of claims 7-13 and 18-26 differs from the disclosure of D15 in that the use of antisense oligonucleotides toward TGF-R<sub>II</sub> or TGF-R<sub>I</sub> for the therapy of Creutzfeldt-Jakob's disease is concerned.

- V.13). The document D17 is regarded as being the closest prior art for the subject-matter of claims 7-13 and 18-26, insofar as these claims are directed (implicitly or

explicitly) to therapy of Multiple Sclerosis and CNS autoimmune disorders, and suggests *a detrimental role for TGF $\beta$  in MS pathology rather than a disease-limiting role* (D17: page 187). Moreover, on page 187, D18 suggest a therapeutical application of TGF- $\beta$  specific antibodies or TGF- $\beta$  receptor antagonists.

The subject-matter of claims 7-13 and 18-26 differs from the disclosure of D17 in that the use of antisense oligonucleotides toward TGF-R<sub>II</sub> or TGF-R<sub>I</sub> for the therapy of Multiple Sclerosis and CNS autoimmune disorders is concerned.

V.14). The document D1 is regarded as being the closest prior art for the subject-matter of claims 7-13 and 18-26, insofar as these claims are directed (implicitly or explicitly) to therapy of CNS and spinal cord trauma, head and spinal trauma, and discloses the use of neutralizing anti-TGF- $\beta$ 1 antibodies and other TGF- $\beta$ 1-neutralizing agents in therapy of diseases wherein neurogenesis or neuroregeneration has a beneficial effect (D1: see relevant passages throughout the entire document).

The subject-matter of claims 7-13 and 18-26 differs from the disclosure of D1 in that the use of antisense oligonucleotides toward TGF-R<sub>II</sub> or TGF-R<sub>I</sub> for the therapy of CNS and spinal cord trauma, head and spinal trauma is concerned.

V.15). The problem to be solved by the present invention may therefore be regarded as the provision of inhibitory agents interfering with the TGF- $\beta$ 1/TGF Receptor(s) signalling, suitable for therapy of Parkinson's disease, Alzheimer's disease, Dementia, Creutzfeldt-Jakob's disease, Multiple Sclerosis, CNS autoimmune disorders, CNS and spinal cord trauma, head and spinal trauma.

V.16). The solution(s) proposed in claims **7-13** and **18-26** of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

- i) the disclosure of documents D1, D2, D3, D15 and D17 suggests that inhibiting TGF- $\beta$ 1 signalling may have beneficial effect in the disorders concerned in these documents;
- ii) antisense technology is well known to the person skilled in the art as a mean to reduce expression of a certain gene, and therapeutical application of antisense molecules are well established in the technical field; as a matter of fact, inhibition of TGF- $\beta$ 1 by means of specific antisense oligonucleotides has also been shown to be effective in increasing the number of multipotent proliferating haematopoietic stem cells (D4: examples 2 and 3). The same document also suggests that this inhibitory effect may be especially useful for neuronal stem cell expansion (D4: page 7, line 24);
- iii) moreover, documents D7, D14, D19 and D20 describe antisense oligonucleotides directed against the TGF- $\beta$  type II receptor as a mean to abrogate TGF- $\beta$ 1 signalling (D7, D14, D19, D20: abstract and relevant passages throughout the entire documents). Document D21 describes that inhibition of expression of the TGF- $\beta$  type II receptor by means of transfection with an antisense the TGF- $\beta$  type II receptor construct abrogates TGF- $\beta$ 1 signalling (D21: abstract and relevant passages throughout the entire document). Document D23 describes an antisense oligonucleotide directed against the TGF- $\beta$  type I receptor as a mean to abrogate TGF- $\beta$ 1 signalling (D23: relevant passages throughout the entire document).

It would therefore be obvious to the person skilled in the art, faced with the problem of inhibiting the TGF $\beta$  / TGF $\beta$  receptor signalling as a therapy of Parkinson's, Alzheimer's disease, Dementia, Creutzfeldt-Jakob's disease, Multiple Sclerosis, CNS autoimmune disorders, CNS and spinal cord trauma, head and spinal trauma, to apply the same antisense technology, thus arriving at a result falling within the scope of present claims **8-11**.

- V.17). The subject-matter of present claims **7-13** and **18-26**, insofar as they are directed to therapy of Alzheimer's disease, Dementia, Parkinson's disease, Creutzfeldt-Jakob's disease, Multiple Sclerosis, CNS autoimmune disorders, CNS and spinal cord trauma, head and spinal trauma, does therefore not involve an inventive step (Article 33(3) PCT).
- V.18). It is known that the other neurodegenerative and neuroinflammatory disorders concerned in claims 11, 13, 24 and 26 could benefit from neurogenesis or neuroregeneration. Therefore, in analogy with the reasoning already expressed for the disorders mentioned above, the entire subject-matter of claims **11, 13, 24** and **26** does also not meet the requirements of Article 33(3) PCT.
- V.19). The industrial applicability of the subject-matter of claims **1-7, 12-20** and **27** is acknowledged (Article 33(4) PCT).
- V.20). For the assessment of the present claims **8-11** and **21-26** on the question whether they are industrially applicable (Article 33(4) PCT), no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treat-

ment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII**

**Certain observations on the international application**

- VIII.1). The terms " variants " and " mimetics " in the claims do not allow to identify unambiguously the matter to which they refer and, as such, the subject-matter associated to these terms does not meet the requirements of Article 6 PCT.
- VIII.2). The common concept underlying the inventions disclosed in present application is that inhibition of  $\text{TGF}\beta$  /  $\text{TGF}\beta$  receptors signalling can have therapeutical applications in neuronal diseases. In this respect, present application provides experimental data involving only one particular antisense molecule (SEQ ID NO:3), targeted toward  $\text{TGF-R}_{II}$ . No further data are provided concerning the other oligonucleotides toward  $\text{TGF-R}_{II}$ , and no technical evidence at all is provided that oligonucleotides toward  $\text{TGF-R}_I$  might as well possess the alleged properties concerned and claimed in present application.

Therefore, it should be remarked that present application does not meet the requirements of Articles 5 and 6 PCT because the subject-matter related to antisense oligonucleotides **other than the ones overlapping with SEQ ID NO:3** is not sufficiently disclosed and supported.

In addition to this previous remark, it should also be objected that, failing this evidence that all the antisense oligonucleotides claimed exert the alleged properties,

these oligonucleotides would therefore be considered as an arbitrary, non inventive choice from a host of oligonucleotides, devoid of any possible effect, among which the person skilled in the art would choose, without intervention of inventive skills, in order to solve the problem of providing further antisense oligonucleotides, regardless of their possible useful effects.

Therefore, failing this evidence that all the antisense oligonucleotides claimed exert the alleged properties, these antisense molecules would also not meet the requirements of Article 33(3) PCT.

VIII-3). In claims 4, 8, 9, 18, 21 and 22, extensive use is made of the options " and/or ". In this case, it is not clear (Article 6 PCT) whether the subject-matter claimed should comprise the oligonucleotide concerned in the first part of the claims **and, in addition**, another *antisense compound comprising a vector*, **or** whether the *antisense compound comprising a vector*, indicated in the second part of the claims, should be considered an alternative to the oligonucleotides indicated in the first part of the claims.

VIII-4). In present claims 14 and 27, the term " TGF- $\beta$ 1/TGF-R signaling " should have been better indicated as " TGF- $\beta$ 1/TGF-R<sub>II</sub> signaling " and " TGF- $\beta$ 1/TGF-R<sub>I</sub> signaling ", respectively.

## New Claims

1. Oligonucleotides selected from the group comprising SEQ ID NO 3 and elongated sequences of SEQ ID NO 3 which can be represented by the following general formula:



wherein X is selected from the group comprising the following oligonucleotides:

ACAGGACGATGTGCAGCGGCCACAGGCCCCCTGAG,  
 CAGGACGATGTGCAGCGGCCACAGGCCCCCTGAG,  
 AGGACGATGTGCAGCGGCCACAGGCCCCCTGAG,  
 GGACGATGTGCAGCGGCCACAGGCCCCCTGAG,  
 GACGATGTGCAGCGGCCACAGGCCCCCTGAG,  
 ACGATGTGCAGCGGCCACAGGCCCCCTGAG,  
 CGATGTGCAGCGGCCACAGGCCCCCTGAG,  
 GATGTGCAGCGGCCACAGGCCCCCTGAG,  
 ATGTGCAGCGGCCACAGGCCCCCTGAG,  
 TGTGCAGCGGCCACAGGCCCCCTGAG,  
 GTGCAGCGGCCACAGGCCCCCTGAG, TGCAGCGGCCACAGGCCCCCTGAG,  
 GCAGCGGCCACAGGCCCCCTGAG, CAGCGGCCACAGGCCCCCTGAG,  
 AGCGGCCACAGGCCCCCTGAG, GCGGCCACAGGCCCCCTGAG,  
 CGGCCACAGGCCCCCTGAG, GGCCACAGGCCCCCTGAG,  
 GCCACAGGCCCCCTGAG, CCACAGGCCCCCTGAG, CACAGGCCCCCTGAG,  
 ACAGGCCCCCTGAG, CAGGCCCCCTGAG, AGGCCCCCTGAG, GGCCCCCTGAG,  
 GCCCCCTGAG, CCCCTGAG, CCCTGAG, CCTGAG, CTGAG, TGAG, GAG,  
 AG, G,

and wherein Z is selected from the group comprising the following oligonucleotides:

GCAGACCCCGCTGCTCGTCATAGACCGAGCCCCC,  
 GCAGACCCCGCTGCTCGTCATAGACCGAGCCCC,  
 GCAGACCCCGCTGCTCGTCATAGACCGAGCCC,  
 GCAGACCCCGCTGCTCGTCATAGACCGAGCC,  
 GCAGACCCCGCTGCTCGTCATAGACCGAGC,  
 GCAGACCCCGCTGCTCGTCATAGACCGAG,  
 GCAGACCCCGCTGCTCGTCATAGACCGA,  
 GCAGACCCCGCTGCTCGTCATAGACCG,  
 GCAGACCCCGCTGCTCGTCATAGACC,

GCAGACCCCGCTGCTCGTCATAGAC, GCAGACCCCGCTGCTCGTCATAGA,  
 GCAGACCCCGCTGCTCGTCATAG, GCAGACCCCGCTGCTCGTCATA,  
 GCAGACCCCGCTGCTCGTCAT, GCAGACCCCGCTGCTCGTCA,  
 GCAGACCCCGCTGCTCGTC, GCAGACCCCGCTGCTCGT,  
 5 GCAGACCCCGCTGCTCG, GCAGACCCCGCTGCTC,  
 GCAGACCCCGCTGCT, GCAGACCCCGCTGC, GCAGACCCCGCTG,  
 GCAGACCCCGCT, GCAGACCCCGC, GCAGACCCCG, GCAGACCC,  
 GCAGACCC, GCAGACC, GCAGAC, GCAGA, GCAG, GCA, GC, G,

10 and wherein X and Z together comprise not more than 34 nucleobases and  
 mimetics thereof

wherein said oligonucleotides are capable of hybridizing sufficiently with the  
 region encompassing the translation initiation codon of the open reading frame  
 15 of the gene encoding TGF-R<sub>II</sub>, and mimetics, variants, salts and optical isomers  
 of said sequence

and with the proviso that said oligonucleotide is not  
 5'-CAGCCCCCGACCCATGGCAG-3'.

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2. Oligonucleotides selected from the group comprising SEQ ID NO 3 to SEQ ID  
 NO 32 and SEQ ID NO 34 to SEQ ID NO 72

wherein said oligonucleotides are capable of hybridizing sufficiently with the  
 region encompassing the translation initiation or termination codon of the open  
 25 reading frame of the gene encoding TGF-R<sub>II</sub>, or a region of the mRNA encoding  
 TGF-R<sub>II</sub> which is a "loop" or "bulge" and which is not part of a secondary  
 structure and mimetics, variants, salts and optical isomers of said sequence.

3. Oligonucleotides according to claim 2 selected from the group comprising:

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SEQ ID NO 3: 5'-CAGCCCCCGACCCATG-3'

SEQ ID NO 34: 5'-CAGCCCCCGACCCATGGCA-3'

SEQ ID NO 35: 5'-CAGCCCCCGACCCATGGC-3'

SEQ ID NO 36: 5'-CAGCCCCCGACCCATGG-3'

SEQ ID NO 41: 5'-GCAGCCCCCGACCCATGGCA-3'

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SEQ ID NO 42: 5'-GCAGCCCCCGACCCATGGC-3'

SEQ ID NO 43: 5'-GCAGCCCCCGACCCATGG-3'

SEQ ID NO 44: 5'-GCAGCCCCCGACCCATG-3'

SEQ ID NO 49: 5'-AGCAGCCCCCGACCCATGGC-3'

SEQ ID NO 50: 5'-AGCAGCCCCCGACCCATGG-3'

SEQ ID NO 51: 5'-AGCAGCCCCCGACCCATG-3'

SEQ ID NO 56: 5'-GAGCAGCCCCCGACCCATGG-3'

SEQ ID NO 57: 5'-GAGCAGCCCCCGACCCATG-3'

SEQ ID NO 62: 5'-TGAGCAGCCCCCGACCCATG-3'.

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4. Pharmaceutical preparation comprising at least one oligonucleotide according to any one of claims 1 – 3 as well as mimetics, variants, salts and optical isomers thereof and/or at least one antisense compound comprising a vector allowing to transcribe at least one said oligonucleotide together with at least one pharmaceutically acceptable carrier, excipient or diluents.

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5. Pharmaceutical preparation according to claim 4, wherein the pharmaceutical preparation is an infusion solution or a solid matrix for continuous release of the active ingredient.

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6. Pharmaceutical preparation according to claim 4 or 5, wherein the pharmaceutical preparation is suitable for local administration into the brain.

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7. Use of at least one oligonucleotide having a sequence at least 80% identical to a sub-sequence of SEQ ID NO 1 or SEQ ID NO 2 comprising 8 to 50 nucleobases, wherein said sequence is capable of hybridizing sufficiently with the region encompassing the translation initiation or termination codon of the open reading frame of the gene encoding TGF-R<sub>II</sub>, or a region of the mRNA encoding TGF-R<sub>II</sub> which is a "loop" or "bulge" and which is not part of a secondary structure and mimetics, variants, salts and optical isomers of said sequence for promoting successful regeneration and functional reconnection of damaged neural pathways.

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8. Use of at least one oligonucleotide according to claim 7 as well as mimetics and variants thereof and/or at least one antisense compound comprising a vector allowing to transcribe at least one said oligonucleotide or a pharmaceutical formulation comprising at least one oligonucleotide according to claim 7 for promoting successful regeneration and functional reconnection of damaged neural pathways.

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9. Use of at least one oligonucleotide according to claim 8 as well as mimetics and variants thereof and/or at least one antisense compound comprising a vector allowing to transcribe at least one said oligonucleotide or a pharmaceutical formulation comprising at least one oligonucleotide according to claim 7 for

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prophylaxis, therapeutic prevention and treatment of neurodegenerative, traumatic / posttraumatic, vascular/hypoxic, neuroinflammatory and postinfectious Central Nervous System disorders, as well as age induced decreases in neuronal stem cell renewal.

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10. Use according to claim 9 for inhibiting TGF-R<sub>II</sub> expression in diseases associated with up-regulated or enhanced TGF-R<sub>II</sub> levels.

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11. Use according to claim 9 or 10, wherein the diseases associated with up-regulated or enhanced TGF-R<sub>II</sub> levels or the neurodegenerative disorders and neuroinflammatory disorders are selected from the group comprising: Alzheimer's diseases, Parkinson's disease, Creutzfeldt Jakob disease (CJD), new variant of Creutzfeldt Jakobs disease (nvCJD), Hallervorden Spatz disease, Huntington's disease, Multisystem Atrophy, Dementia, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, Spinal Muscular Atrophy, Spinocerebellar Atrophies (SCAs), or other Motor Neuron Disorders, schizophrenia, affective disorders, major depression, meningoencephalitis, bacterial meningoencephalitis, viral meningoencephalitis, CNS autoimmune disorders, Multiple Sclerosis (MS), acute ischemic / hypoxic lesions, stroke, CNS and spinal cord trauma, head and spinal trauma, arteriosclerosis, atherosclerosis, microangiopathic dementia, Binswanger' disease (Leukoaraiosis), retinal degeneration, cochlear degeneration, macular degeneration, cochlear deafness, AIDS-related dementia, retinitis pigmentosa, fragile X-associated tremor/ataxia syndrome (FXTAS), progressive supranuclear palsy (PSP), striatonigral degeneration (SND), olivopontocerebellar degeneration (OPCD), Shy Drager syndrome (SDS), age dependant memory deficits, neurodevelopmental disorders associated with dementia, Down's Syndrome, synucleinopathies, Superoxide Dismutase Mutations, Trinucleotide Repeat Disorders, trauma, hypoxia, vascular diseases, vascular inflammations, CNS-ageing.

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12. Use according to claim 9 for inhibiting TGF- $\beta$  activity in diseases associated with up-regulated or enhanced signaling of TGF-R<sub>II</sub>.

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13. Use according to claim 9 or 12, wherein the diseases associated with up-regulated or enhanced signaling of TGF-R<sub>II</sub> or the neurodegenerative disorders and neuroinflammatory disorders are selected from the group comprising: Alzheimer's diseases, Parkinson's disease, Creutzfeldt Jakob disease (CJD), new variant of Creutzfeldt Jakobs disease (nvCJD), Hallervorden Spatz disease, Huntington's disease, Multisystem Atrophy, Dementia, Frontotemporal Dementia,

Amyotrophic Lateral Sclerosis, Spinal Muscular Atrophy, Spinocerebellar Atrophies (SCAs), or other Motor Neuron Disorders, schizophrenia, affective disorders, major depression, meningoencephalitis, bacterial meningoencephalitis, viral meningoencephalitis, CNS autoimmune disorders, Multiple Sclerosis (MS), acute ischemic / hypoxic lesions, stroke, CNS and spinal cord trauma, head and spinal trauma, arteriosclerosis, atherosclerosis, microangiopathic dementia, Binswanger' disease (Leukoaraiosis), retinal degeneration, cochlear degeneration, macular degeneration, cochlear deafness, AIDS-related dementia, retinitis pigmentosa, fragile X-associated tremor/ataxia syndrome (FXTAS), progressive supranuclear palsy (PSP), striatonigral degeneration (SND), olivopontocerebellar degeneration (OPCD), Shy Drager syndrome (SDS), age dependant memory deficits, neurodevelopmental disorders associated with dementia, Down's Syndrome, synucleinopathies, Superoxide Dismutase Mutations, Trinucleotide Repeat Disorders, trauma, hypoxia, vascular diseases, vascular inflammations, CNS-ageing.

14. Method for identifying a compound interfering with (a) the biological activity of TGF- $R_{II}$  or the expression of TGF- $R_{II}$ , or (b) the TGF- $\beta 1$ /TGF-R signaling, comprising the steps of:

(a) incubating a candidate compound with a test system comprising TGF- $\beta 1$  and neuronal precursor cells; and

(b) assaying the expression of active TGF receptors or the proliferation of the neuronal precursor cells; wherein

(c) an abolition of (i) the suppression of expression of active TGF receptors or (ii) suppression of proliferation of the neuronal precursor cells compared to the test system in the absence of said test compound is indicative of the presence of a candidate compound having the desired properties.

15. Oligonucleotides having a sequence at least 80% identical to a sub-sequence of SEQ ID NO 94 or SEQ ID NO 95 or SEQ ID NO 96 comprising 8 to 50 nucleobases, wherein said sequence is capable of hybridizing sufficiently with the region encompassing the translation initiation or termination codon of the open reading frame of the gene encoding TGF- $R_I$ , or a region of the mRNA encoding TGF- $R_I$  which is a "loop" or "bulge" and which is not part of a secondary structure and mimetics, variants, salts and optical isomers of said sequence.

16. Oligonucleotides having a sub-sequence of SEQ ID NO 94 or SEQ ID NO 95 or SEQ ID NO 96 comprising 8 to 50 nucleobases and mimetics, variants, salts and optical isomers thereof.

- 5 17. Oligonucleotides according to claim 16, selected from the group comprising
- 10 SEQ ID NO 73: 5'-ATGTGAAGATGGGCAAGACC-3'
- SEQ ID NO 74: 5'-ATCTCCATGTGAAGATGGGC-3'
- SEQ ID NO 75: 5'-AACGGCCTATCTCGAGGAAT-3'
- SEQ ID NO 76: 5'-AACATCGTCGAGCAATTTCC-3'
- SEQ ID NO 77: 5'-AATCCAACCTCCTTTGCCCTT-3'
- SEQ ID NO 78: 5'-AAACCTGAGCCAGAACCTGA-3'
- SEQ ID NO 79: 5'-AGGGCGATCTAATGAAGGGT-3'
- SEQ ID NO 80: 5'-AGTGCACAGAAAGGACCCAC-3'
- SEQ ID NO 81: 5'-ACACTGGTCCAGCAATGACA-3'
- 15 SEQ ID NO 82: 5'-TTCCTGTTGACTGAGTTGCG-3'
- SEQ ID NO 83: 5'-CACTCTGTGGTTTGGAGCAA-3'
- SEQ ID NO 84: 5'-CAAGGCCAGGTGATGACTTT-3'
- SEQ ID NO 85: 5'-CACACTGGTCCAGCAATGAC-3'
- SEQ ID NO 86: 5'-CTGACACCAACCAGAGCTGA-3'
- 20 SEQ ID NO 87: 5'-CTCTGCCATCTGTTTGGGAT-3'
- SEQ ID NO 88: 5'-TCAAAAAGGGATCCATGCTC-3'
- SEQ ID NO 89: 5'-TGACACCAACCAGAGCTGAG-3'
- SEQ ID NO 90: 5'-TGATGCCTTCCTGTTGACTG-3'
- SEQ ID NO 91: 5'-TTCCTGTTGACTGAGTTGCG-3'
- 25 SEQ ID NO 92: 5'-TTCTCCAAATCGACCTTTGC-3'
- SEQ ID NO 93: 5'-GGAGAGTTCAGGCAAAGCTG-3'

30 18. Pharmaceutical preparation comprising at least one oligonucleotide according to any one of claims 15 –17 as well as mimetics, variants, salts and optical isomers thereof and/or at least one antisense compound comprising a vector allowing to transcribe at least one said oligonucleotide together with at least one pharmaceutically acceptable carrier, excipient or diluents.

35 19. Pharmaceutical preparation according to claim 18, wherein the pharmaceutical preparation is an infusion solution or a solid matrix for continuous release of the active ingredient.

20. Pharmaceutical preparation according to claim 18 or 19, wherein the pharmaceutical preparation is suitable for local administration into the brain.

21. Use of at least one oligonucleotide according to any one of claims 15 to 17 as well as mimetics and variants thereof and/or at least one antisense compound comprising a vector allowing to transcribe at least one said oligonucleotide or a pharmaceutical formulation according to any one of claim 18 to 20 for promoting successful regeneration and functional reconnection of damaged neural pathways.
22. Use of at least one oligonucleotide according to any one of claims 15 to 17 as well as mimetics and variants thereof and/or at least one antisense compound comprising a vector allowing to transcribe at least one said oligonucleotide or a pharmaceutical formulation according to any one of claim 18 to 20 for prophylaxis, therapeutic prevention and treatment of neurodegenerative, traumatic / posttraumatic, vascular/hypoxic, neuroinflammatory and postinfectious Central Nervous System disorders, as well as age induced decreases in neuronal stem cell renewal.
23. Use according to claim 22 for inhibiting TGF-R<sub>I</sub> expression in diseases associated with up-regulated or enhanced signaling of TGF-R<sub>I</sub>.
24. Use according to claim 22 or 23, wherein the diseases associated with up-regulated or enhanced signaling of TGF-R<sub>I</sub> or the neurodegenerative disorders and neuroinflammatory disorders are selected from the group comprising: Alzheimer's diseases, Parkinson's disease, Creutzfeldt Jakob disease (CJD), new variant of Creutzfeldt Jakobs disease (nvCJD), Hallervorden Spatz disease, Huntington's disease, Multisystem Atrophy, Dementia, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, Spinal Muscular Atrophy, Spinocerebellar Atrophies (SCAs), or other Motor Neuron Disorders, schizophrenia, affective disorders, major depression, meningoencephalitis, bacterial meningoencephalitis, viral meningoencephalitis, CNS autoimmune disorders, Multiple Sclerosis (MS), acute ischemic / hypoxic lesions, stroke, CNS and spinal cord trauma, head and spinal trauma, arteriosclerosis, atherosclerosis, microangiopathic dementia, Binswanger' disease (Leukoaraiosis), retinal degeneration, cochlear degeneration, macular degeneration, cochlear deafness, AIDS-related dementia, retinitis pigmentosa, fragile X-associated tremor/ataxia syndrome (FXTAS), progressive supranuclear palsy (PSP), striatonigral degeneration (SND), olivopontocerebellar degeneration (OPCD), Shy Drager syndrome (SDS), age dependant memory deficits, neurodevelopmental disorders associated with

dementia, Down's Syndrome, synucleinopathies, Superoxide Dismutase Mutations, Trinucleotide Repeat Disorders, trauma, hypoxia, vascular diseases, vascular inflammations, CNS-ageing.

- 5 25. Use according to claim 22 for inhibiting TGF- $\beta$  activity in diseases associated with up-regulated or enhanced TGF- $\beta$  levels.
- 10 26. Use according to claim 22 or 25, wherein the diseases associated with up-regulated or enhanced TGF- $\beta$  levels or the neurodegenerative disorders and neuroinflammatory disorders are selected from the group comprising: Alzheimer's diseases, Parkinson's disease, Creutzfeldt Jakob disease (CJD), new variant of Creutzfeldt Jakobs disease (nvCJD), Hallervorden Spatz disease, Huntington's disease, Multisystem Atrophy, Dementia, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, Spinal Muscular Atrophy, Spinocerebellar Atrophies (SCAs), or other Motor Neuron Disorders, schizophrenia, affective disorders, major depression, meningoencephalitis, bacterial meningoencephalitis, viral meningoencephalitis, CNS autoimmune disorders, Multiple Sclerosis (MS), acute ischemic / hypoxic lesions, stroke, CNS and spinal cord trauma, head and spinal trauma, arteriosclerosis, atherosclerosis, microangiopathic dementia, Binswanger' disease (Leukoaraiosis), retinal degeneration, cochlear degeneration, macular degeneration, cochlear deafness, AIDS-related dementia, retinitis pigmentosa, fragile X-associated tremor/ataxia syndrome (FXTAS), progressive supranuclear palsy (PSP), striatonigral degeneration (SND), olivopontocerebellar degeneration (OPCD), Shy Drager syndrome (SDS), age dependant memory deficits, neurodevelopmental disorders associated with dementia, Down's Syndrome, synucleinopathies, Superoxide Dismutase Mutations, Trinucleotide Repeat Disorders, trauma, hypoxia, vascular diseases, vascular inflammations, CNS-ageing.
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- 25
- 30 27. Method for identifying a compound interfering with (a) the biological activity of TGF- $R_1$  or the expression of TGF- $R_1$ , or (b) the TGF- $\beta$ 1/TGF-R signaling, comprising the steps of:
- 35 (a) incubating a candidate compound with a test system comprising TGF- $\beta$ 1 and neuronal precursor cells; and
- (b) assaying the expression of active TGF receptors or the proliferation of the neuronal precursor cells;
- wherein
- (c) an abolition of (i) the suppression of expression of active TGF receptors or (ii) suppression of proliferation of the neuronal precursor cells

compared to the test system in the absence of said test compound is indicative of the presence of a candidate compound having the desired properties.